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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/461,090	12/14/99	ULLRICH	A P564-9051

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EXAMINER	
LU,F	
ART UNIT	**PAPER NUMBER**
1655	7

DATE MAILED: 09/13/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/461,090	Applicant(s) Ullrich et al.,
	Examiner Frank Lu	Group Art Unit 1655

☒ Responsive to communication(s) filed on *Dec 14, 1999* .

☐ This action is **FINAL.**

☒ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-20* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1 and 4-20* is/are rejected.

☒ Claim(s) *2 and 3* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Location of Application

1. The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1655.

Drawings

2. The drawings are objected to for reasons as stated on FORM PTO-948 (Rev. 8-98). Applicant is required to submit a proposed drawing correction in reply to this Office action. However, formal correction of the noted defect can be deferred until the application is allowed by the examiner.

Claim Objections

3. Claims 5 is objected to because of the following informalities: Note that "EGFR" is abbreviations. They can only be used after each phrase appears once. Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

> person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for modulating growth-factor activation comprising contacting a cell or an organism which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction in *in vitro*, does not reasonably provide enablement for using a method for modulating growth-factor activation comprising contacting a cell or an organism which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction in the prevention or treatment of disorders such as cancer or asthma which is associated with pathologically enhanced growth-factor receptor activation wherein said modulator is administrated as a pharmaceutically acceptable composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Note that claims 2-19 are dependent on claim 1.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*, 230 USPQ 547. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Quantity of Experimentation Necessary & The Amount of Direction or Guidance Provided

Claims 1 and 17-19 in this instant application are directed to a method for modulating growth-factor activation comprising contacting a cell or an organism which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction.

The claims have sufficient breadth of scope so to encompass using a method for modulating growth-factor activation comprising contacting a cell or an organism which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction in the prevention or treatment of disorders such as cancer or asthma which is associated with pathologically enhanced growth-factor receptor activation wherein said modulator is administrated as a pharmaceutically acceptable composition. The specification (pages 9-17) provides adequate guidance for a method for modulating growth-factor activation comprising contacting a cell or an organism which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction in *in vitro*. However, although the specification (pages 3-6) describes the possibility for the prevention and treatment of disorder such as cancer administering active agents such as metalloprotease as a pharmaceutically acceptable composition, the specification does not provide adequate guidance for using a method for modulating growth-factor activation comprising contacting a cell or an organism which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction in the prevention or treatment of disorders such as cancer or asthma which is associated with pathologically enhanced growth-factor receptor wherein said modulator

is administered as a pharmaceutically acceptable composition which the claims are directed to. These guidances include but not limit to: (1) how to organize active agents such as metalloprotease into a pharmaceutically acceptable composition; and (2) how to apply the results from *in vitro* experiments into human. For example, how to determine useful dose of an active agent in in a pharmaceutically acceptable composition in human without a preclinical trial.

With the specification exemplifying a method for modulating growth-factor activation comprising contacting a cell or an organism which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction, and suggesting other treatment, the skilled artisan is left to figure out how to use a method for modulating growth-factor activation comprising contacting a cell or an organism which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction in the prevention or treatment of disorders such as cancer or asthma which is associated with pathologically enhanced growth-factor receptor activation wherein said modulator is administrated as a pharmaceutically acceptable composition.

Since the specification does not provide adequate guidance for the prevention or treatment of disorders such as cancer or asthma as described above, it would take the skilled artisans several years to figure out the experimental conditions with little, if any, variable expectation of success. Such efforts constitute undue experimentation. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen*

> *Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In order to practice the full scope of the invention, the skilled artisan will have to resolve but not limit to: (1) how to organize active agents such as metalloprotease into a pharmaceutically acceptable composition; and (2) how to apply the results from *in vitro* experiments into human. For example, how to determine useful dose of an active agent in in a pharmaceutically acceptable composition in human without a preclinical trial. It would require several years for the skilled artisan to resolve each of these issues, assuming that such is achievable.

The Presence or Absence of Working Examples

The specification (pages 9-17) provides a working example to show that EGF receptor transactivation by G-protein-coupled receptors requires metalloproteinase cleavage of proHB-EGF.

The Nature of the Invention

The invention relates to a method for modulating growth-factor activation comprising contacting a cell or an organism which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction.

The State of the Prior Art

At the time of filling, a method for modulating growth-factor activation comprising contacting a cell or an organism which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction (Daub *et al.*, EMBO. J. 16, 7032-7044, December 1997). Using a method for modulating growth-factor activation comprising contacting a cell or an organism which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction in the prevention or treatment of disorders such as cancer or asthma which is associated with pathologically enhanced growth-factor receptor activation wherein said modulator is administrated as a pharmaceutically acceptable composition is a novel and an undeveloped area of the art.

The Relative Skill of Those in the Art

The relative skill of those in the art to which the invention most closely pertains is high, on par with those which hold a Ph.D. in biochemistry.

The Predictability or Unpredictability of the Art

Based on the limited guidance provided by the specification (page 3-6 and 9-17), a skilled artisan can use a method for modulating growth-factor activation comprising contacting a cell or an organism which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction in *in vitro*. However, it is unpredictable whether a skilled artisan can use a method for modulating growth-factor activation comprising contacting a cell or an organism which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction in the prevention or treatment of disorders such as cancer or asthma which is associated with pathologically enhanced growth-factor receptor activation wherein said modulator is administrated as a pharmaceutically acceptable composition because the specification does not provide (1) how to organize active agents such as metalloprotease into a pharmaceutically acceptable composition; and (2) how to apply the results from *in vitro* experiments into human. For example, how to determine useful dose of an active agent in in a pharmaceutically acceptable composition in human without a preclinical trial.

The predictability of the art is low. Further, the claimed invention relates directly to matters of physiology and chemistry which are inherently unpredictable and as such, require greater levels of enablement. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

The Breadth of the Claims

The claims encompass a method of a method for modulating any kind of growth-factor activation comprising contacting any kind of cell or organism which contains any kind of growth-factor receptor capable of being activated with any kind of modulator of G-protein mediated signal transduction.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 17, and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Regarding claim 17, the phrase "for example (e.g.)" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Note that claim 17 is dependent on claim 1.

9. The term "pharmaceutically acceptable composition" in claim 19 is a relative term which renders the claim indefinite. The term "pharmaceutically acceptable composition" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree,

and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Note that claim 19 is dependent on claim 1.

Claim Rejections - 35 U.S.C. § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1, 4, 5, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Daub *et al.*, (EMBO. J. 16, 7032-7044, December 1997).

Daub *et al.*, teach signal characteristics of G protein-transactivated EGF receptor. As acknowledged by Daub *et al.*, the epidermal growth factor receptor (EGFR) is known as an essential link in the GPCR-mediated MAPK activation pathway in Rat-1 fibroblasts treated with the GPCR agonists ET-1, LPA or thrombin (page 7032, right column, second paragraph). This cross-talk pathway is also established in different cell types such as HaCaT keratinocytes, primary mouse astrocytes and COS-7 cells (page 7032, abstract). In this study, different cell types were stimulated with different modulator which include endogenous GPCR signal events such as LPA, thrombin, TRP, and EGR as described in claims 1, 4, 5, and 20. After lysing the cells, EGFR was immunoprecipitated using polyclonal anti-EGFR antibody. Immunoblotting was done with anti-phosphotyrosine mAb, followed by reprobing with anti-EGFR antibody (page 7033, the Figure legend of Figure 1). As shown in Figure 1A, stimulation of human HaCaT keratinocytes with

thrombin or LPA resulted in enhanced tyrosine phosphorylation of endogenous EGFR. In addition, thrombin or extracellularly applied ATP triggered a comparable response in primary mouse astrocytes (Figure 1B). Thrombin and LPA were also effective in COS-7 cells, where these GPCR ligands stimulated tyrosine phosphorylation of endogenous EGFR to a similar extent as 1-3 ng/ml EGF (Figure 1C) (page 7033, left column, second paragraph). This prior art meets the limitation of the claims.

Claim Rejections - 35 U.S.C. § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Daub et al., (EMBO. J. 16, 7032-7044, December 1997) in view of Dong *et al.*, (Proc. Natl. Acad. Sci. USA,

96, 6235-6240, May 1999) and in further view of Khandaker *et al.*, (Blood 93, 2173-2185, April 1999).

The teachings of Daub *et al.*, have been summarized previously, *supra.* This prior art contains embodiments/limitation of claims 1, 4, 5, and 16. .

Daub *et al.*, do not disclose that metalloprotease-mediated ligand release regulates through the epidermal growth factor receptor and metalloprotease inhibitor.

Dong *et al.*, teach metalloprotease-mediated ligand release regulates autocrine signaling through the epidermal growth factor receptor. As acknowledged by Dong *et al.*, ligands that activate the epidermal growth factor receptor (EGFR) are synthesized as membrane-anchored precursors that appear to be proteolytically released by members of the ADAM family of metalloproteases. This membrane-anchored EGFR ligands are thought to be biologically. In this study, they used metalloprotease inhibitors to block EGFR ligand release from human mammary epithelial cells. These cells express both transforming growth factor α and amphiregulin and require autocrine signaling through the EGFR (extracellular domain) for proliferation and migration. They found that a metalloprotease inhibitor, batimastat (see page 6236, Figure 1), reduced cell proliferation in direct proportion to their effect on transforming growth factor α release. This metalloprotease inhibitor also reduced growth of EGF-responsive tumorigenic cell lines and were synergistic with the inhibitory effects of antagonistic EGFR antibodies. Blocking release of EGFR ligands also strongly inhibited autocrine activation of the EGFR and reduced both the rate and persistence of cell migration. The effects of this metalloprotease inhibitor could be reversed by either adding exogenous EGF or by expressing an artificial gene for EGF that

lacked a membrane-anchoring domain (page 6235, abstract). This prior art contains some of embodiments/limitations of claims 1 -3 and 6-15.

Dong *et al.*, do not disclose transactivation of the EGF receptor in signaling by G-protein-coupled receptors and EGF.

Khandaker *et al.*, teach the effects of metalloproteinases in lipopolysaccharide- and tumor necrosis factor-α-mediated regulation of CXCR1 and CXCR2 chemokine receptor expression (page 2173, abstract). Note that both CXCR1 and CXCR2 are neutrophil-specific G-protein-coupled chemokine receptors. As acknowledged by Khandaker *et al.*, various studies have recently implicated the activity of metalloproteinases and serine proteinases in the cleavage of cell surface molecules (page 2173, right column, second paragraph). To investigate whether proteolytic cleavage was the mechanism responsible for LPS- and TNF induced downmodulation of IL-8 receptors, we tested a panel of proteinase inhibitors. They found that the downmodulation of CXCR1 and CXCR2 by LPS and TNF- was most dramatically inhibited by an metalloproteinase inhibitor, 1,10-phenanthroline (see Figures 2A and 2B in page 2176 and Figure 4 in page 2179). This metalloproteinase inhibitor also blocked the release of CXCR1 cleavage fragments into the cell supernatants of LPS- and TNF--stimulated neutrophils (see page 2179, Figure 5). This prior art contains some of embodiments/limitations of claims 1, 6-8, and 12-14.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to have studied the effect of metalloproteinase inhibitors in transactivation of the EGF receptor in signaling by G-protein-coupled receptors as suggested by Daub *et al.*, and Khandaker *et al.*, using the metalloproteinase inhibitors to block the release of precursors of EGF receptor

ligand anchored on cell membranes as suggested by Dong *et al.*. The methods provided by Khandaker *et al.*, and Dong *et al.* would have motivated one having ordinary skill in the art to study the inhibition of proHB-EGF cleavage by a metalloproteinase inhibitor such as batimastat in transactivation of the EGF receptor in signaling by G-protein-coupled receptors because the downmodulation of neutrophil-specific G-protein-coupled chemokine receptors such as CXCR1 and CXCR2 was shown to be most dramatically inhibited by a metalloproteinase inhibitor-1,10-phenanthroline and another metalloprotease inhibitor- batimastat was shown to block EGFR ligand, transforming growth factor α, release from human mammary epithelial cells. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to combine these prior arts together because all of these prior arts are known and are easy to use.

Conclusion

14. No Claim is allowed.

15. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
September 1, 2000

B. L. Sisson

BRADLEY L. SISSON
PRIMARY EXAMINER
GROUP 1800

9/11/00